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Digestion, absorption, fermentation, and metabolism of functional sugar substitutes and their available energy*

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Abstract: Many kinds of oligosaccharides and sugar alcohols have been newly developed as bulking sugar substitutes that have beneficial health effects. A sugar substitute that is not digested and absorbed in the small intestine reaches the large intestine, where it is completely fermented by intestinal bacteria and produces short-chain fatty acids, which are converted to energy. The available energy of a nondigestible sugar substitute, which is completely fermented by intestinal microbes, is estimated as approximately 2 kcal/g.

On the other hand, a sufficiently high ingestion of nondigestible sugar substitutes regularly causes overt diarrhea in human and animals. However, the diarrhea disappears within a few days because intestinal microbes, which readily utilize these saccharides, increase during ingestion. The maximum permissible dose, by which transitory diarrhea is not caused by the ingestion of nondigestible sugar substitutes, is estimated as approximately 0.3 g per kg body weight in single ingestion for Japanese adults. The value is varied by some factors, such as separate ingestion, repeat ingestion, test substance, and body condition, etc.

SUMMARY OF SUGAR SUBSTITUTES WITH BENEFICIAL HEALTH EFFECTS

Many kinds of oligosaccharides and sugar alcohols have been newly developed as bulking sugar substitutes that have beneficial health effects (Table 1). The specific physiological functions are

- to offer lower available energy,
- to save insulin secretion from the pancreas,
- to improve intestinal microflora,
- to be noncariogenic,
- and to stimulate intestinal mineral absorption [1,2].

Most of these sugar substitutes, except for disaccharide alcohols, are constituents of natural plant foods. However, physiologically functional oligosaccharides are currently mass-produced from sucrose, lactose, maltose, and starch derivatives, using specific microbial enzymes. Sugar alcohols, except for erythritol, are produced by hydrogenation of maltose, lactose, palatinose, glucose, xylose and partially hydrolyzed starch derivatives.

In the experiments of hydrolyzing activity of several oligosaccharides and sugar alcohols using rat intestinal brush border membrane vesicle (BBMV), 1-kestose, nystose, raffinose, lactulose, lactitol, gentio-oligosaccharide, and galacto-oligosaccharide were not hydrolyzed [3,4]. Galactosyl-sucrose, isomaltitol, maltitol, and cellobiose were scarcely hydrolyzed, and panose and palatinose, trehalose, and

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Table 1 Summary of sugar substitutes with beneficial health effects.**1. Oligosaccharides**

- Galactosyl-sucrose [$\text{Gal}_{\beta 1-4}\text{G}_{\alpha 1-2}\text{F}$] (35–65)
 Theandrose [$\text{G}_{\alpha 1-6}\text{G}_{\alpha 1-2}\text{F}$] (ca. 50)
 4'Galacto-oligosaccharide [$(\text{Gal}_{\beta 1})_n\text{Gal}_{\beta 1-4}\text{G}$] $n = 1-3$ (20–40)
 6'Galacto-oligosaccharide [$(\text{Gal}_{\beta 1})_n\text{Gal}_{\beta 1-4}\text{G}$] $n = 1-5$ (20–40)
 Xylo-oligosaccharide [$\text{Xyl}_{\beta 1-4}\text{Xyl}_{\beta 1}(\text{Xyl})_n$] $n = 1-4$ (ca. 50)
 Fructo-oligosaccharides (30–60)
 a mixture of kestose [$\text{G}_{\alpha 1-2}\text{F}_{1-2}\beta\text{F}$], nystose [$\text{G}_{\alpha 1-2}\text{F}_{1-2}\beta\text{F}_{1-2}\beta\text{F}$] and
 fructofuranosyl nystose [$\text{G}_{\alpha 1-2}\text{F}_{1-2}\beta\text{F}_{1-2}\beta\text{F}_{1-2}\beta\text{F}$]
 Isomalto-oligosaccharides (ca. 50)
 a mixture of isomaltotriose [$\text{G}_{\alpha 1-6}\text{G}_{\alpha 1-6}\text{G}$], panose [$\text{G}_{\alpha 1-4}\text{G}_{\alpha 1-6}\text{G}$], isomaltose
 [$\text{G}_{\alpha 1-6}\text{G}$], maltose [$\text{G}_{\alpha 1-4}\text{G}$], and glucose [G]
 Gentio-oligosaccharides (bitter)
 a mixture of β -glucotetraose [$\text{G}_{\beta 1-6}\text{G}_{\beta 1-6}\text{G}_{\beta 1-6}\text{G}$], β -glucotriose [$\text{G}_{\beta 1-6}\text{G}_{\beta 1-6}\text{G}$],
 β -glucobiose [$\text{G}_{\beta 1-6}\text{G}$], and monosaccharides [G, F]
 Soybean-oligosaccharides (ca. 70)
 a mixture of raffinose [$\text{G}_{\alpha 1-6}\text{G}_{\alpha 1-2}\text{F}$], stachyose [$\text{Gal}_{\alpha 1-6}\text{Gal}_{\alpha 1-6}\text{G}_{\alpha 1-2}\text{F}$], sucrose
 [$\text{G}_{\alpha 1-2}\text{F}$], and monosaccharides [G, F]
 Coupling sugar (50–60)
 a mixture of glucosyl-sucrose [$\text{G}_{\alpha 1-4}\text{G}_{\alpha 1-2}\text{F}$], maltosyl-sucrose
 [$\text{G}_{\alpha 1-4}\text{G}_{\alpha 1-4}\text{G}_{\alpha 1-2}\text{F}$], and monosaccharides [G, F]

2. Disaccharides

- Trehalose [$\text{G}_{\alpha 1-1}\text{G}$] (50)
 Cellobiose [$\text{G}_{\beta 1-4}\text{G}$] (30)
 Lactulose [$\text{G}_{\beta 1-4}\text{F}$] (60–70)
 Palatinose [$\text{G}_{\alpha 1-6}\text{F}$] (37–45)

3. Sugar Alcohols

- Erythritol (75–80)
 Xylitol (ca. 100)
 Sorbitol (50–60)
 Maltitol [$\text{G}_{\alpha 1-4}\text{Sol}$] (80–95)
 Lactitol [$\text{Gal}_{\beta 1-4}\text{Sol}$] (30–40)
 Palatinit (30–40)
 a mixture of isomaltitol [$\text{G}_{\alpha 1-6}\text{Sol}$] and glucopyranosyl- $\alpha_{1,6}$ -mannitol [$\text{G}_{\alpha 1-6}\text{Man}$]

Abbreviations: G: glucose; F: fructose; Xly: xylitol; Gal: galactose; Sol: sorbitol; Man: mannitol; (): sweetness; % of sucrose.

nigerose were hydrolyzed more quickly than lactose. Hydrolyzing activity for maltose was about 3 to 4 times that of sucrose and 4 to 5 times that for isomaltose. The hydrogenation of mono- and disaccharides increased the resistance for absorption and digestion, compared with that of the original saccharides. Their sweetness is increased by the hydrogenation of the original saccharides [3,4]. These sugar substitutes have some unique properties for digestion, absorption, and metabolism.

CHARACTERISTICS AND METABOLISM OF NONDIGESTIBLE FRUCTO-OLIGOSACCHARIDE

Recent studies on the utilization and physiological function of newly developed sugar substitutes show that nondigestible oligosaccharides and sugar alcohols are metabolized via intestinal bacteria, and these

properties, which are nondigestible and fermentable, are closely related to their special physiological functions. Fructo-oligosaccharide (the other name is Neosugar) is a typical nondigestible oligosaccharide that is metabolized through a unique pathway.

Fructo-oligosaccharide is a mixture of 1-kestose, nystose, and fructo-furanosyl nystose. These compounds are contained in several plants, but it is manufactured enzymatically from sucrose, at present. 1-Kestose (GF2) and nystose (GF3), which are components of fructo-oligosaccharide, were not hydrolyzed by any digestive enzymes of rat small intestinal mucosa homogenate, while maltose and sucrose were readily hydrolyzed [5]. Furthermore, when ^{14}C -fructo-oligosaccharide was injected intravenously into rats, it was readily excreted into the urine without any degradation [5].

These results suggest that orally administered fructo-oligosaccharide cannot metabolize apparently and do not contribute as an energy source of the host. However, when fructo-oligosaccharide was orally administered to animals, it was metabolized spontaneously to carbon dioxide as the similar results obtained with digestible sucrose.

When ^{14}C -fructo-oligosaccharide was orally administered to conventional rats, about 60 % of the total radioactivity administered was exhaled as carbon dioxide within 24 h (Fig. 1) [1,4]. The recovery of radioactivity was similar to the results obtained with ^{14}C -sucrose, in spite of the fact that fructo-oligosaccharide is not hydrolyzed by any intestinal enzymes. But there was a delay of about 3 h in carbon dioxide release in animals that were administered with ^{14}C -fructo-oligosaccharide, as compared to rats fed with ^{14}C -sucrose.

Furthermore, when ^{14}C -fructo-oligosaccharide was administered orally to antibiotic-treated and germ-free rats, the conversion of fructo-oligosaccharide to carbon dioxide was strongly inhibited (Fig. 1) [1,5]. These results strongly suggest that nondigestible fructo-oligosaccharide is metabolized via intestinal bacteria.

In addition, when ^{14}C -fructo-oligosaccharide was injected directly into the cecum of conventional rats, it was metabolized spontaneously to carbon dioxide, and the time sequence of carbon dioxide

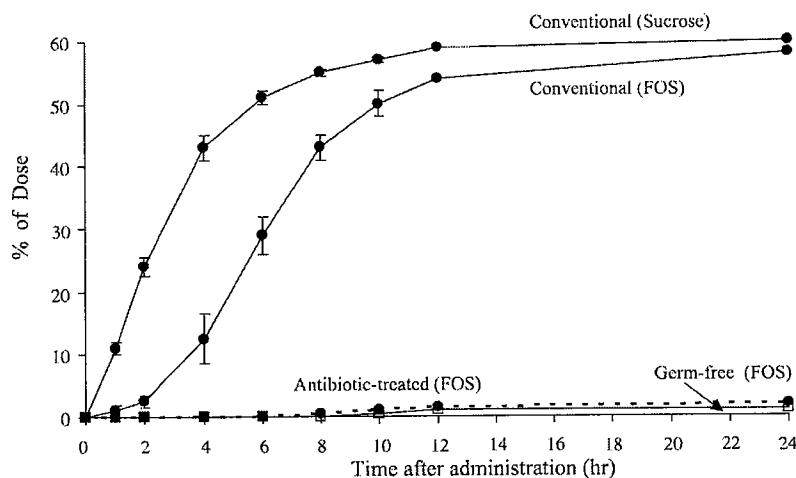


Fig. 1 Cumulative expired $^{14}\text{CO}_2$ after oral administration of [^{14}C]FOS or [^{14}C]sucrose to conventional, antibiotic-treated, and germ-free rats. [^{14}C]FOS (74 kBq per 4 mg/0.4 mL) dissolved in 9 g of NaCl in 1 L of distilled water was administered orally to conventional, antibiotic-treated, and germ-free rats (body weight about 230 g). Immediately after dosing, rats were transferred to individual metabolic cages that had a closed system made of glass; (111 kBq per 4 mg/0.4 mL) was used as the control digestible sugar. Each point represents the mean \pm SEM for three to four rats. FOS: fructo-oligosaccharides.

excretion showed a similar shape as that of orally administered sucrose [5]. This time, the intact fructo-oligosaccharide was not detected in the feces of these rats. These results demonstrate that intestinal bacteria is concerned with the degradation of fructo-oligosaccharide, and it takes 3 to 4 h to reach the large intestine after oral ingestion in rats.

When ^{14}C -fructo-oligosaccharide was incubated anaerobically with the cecal content of conventional rats, short-chain fatty acids such as acetic acid, propionic acid, butyric acid and valeric acid, and carbon dioxide were readily produced, and a part of the radioactivity was incorporated into the component of intestinal bacteria (Table 2) [5]. These results support the fact that sugar substitutes administered orally are metabolized to short-chain fatty acid, carbon dioxide, and others by intestinal microbes and further metabolized in the body.

Furthermore, when ^{14}C -short-chain fatty acids such as lactic acid, acetic acid, propionic acid, and butyric acid were injected directly into the cecum of conventional rats, they were readily absorbed and metabolized to carbon dioxide. The time sequence of carbon dioxide excretion showed a shape similar to that of fructo-oligosaccharide, which was directly injected into the cecum [5]. These results support the fact that short-chain fatty acids, which are produced by fermentation, are readily absorbed from the lower intestine and contribute as an energy source for the host.

Table 2 ^{14}C -products from $[\text{U-}^{14}\text{C}]\text{FOS}$ after incubation with cecal contents from conventional rats fed a diet with or without FOS^a.

^{14}C -products	Cecal contents	
	FOS-free diet	FOS diet
	% of total radioactivity in the medium	
$^{14}\text{CO}_2$	12.5 \pm 3.4	11.8 \pm 3.8
^{14}C in microbes ^b	6.2 \pm 0.2	10.8 \pm 1.6 ^c
^{14}C -volatile fatty acids	66.1 \pm 2.2	71.5 \pm 6.6
Acetic acid	13.9 \pm 3.0	17.9 \pm 1.2
Propionic acid	15.8 \pm 3.8	18.9 \pm 10.8
Butyric acid	28.7 \pm 3.6	29.3 \pm 6.2
Valeric acid	4.8 \pm 1.6	5.4 \pm 2.6
Others	11.8 \pm 4.6	5.2 \pm 5.2
Recovery	95.8 \pm 1.8	98.6 \pm 4.0

^aEach value represents the mean SD of four rats with duplicate determinations.

^b ^{14}C in microbes shows that the radioactivity was incorporated into the precipitate of the reactant.

^cSignificantly different from the FOS-free diet group at $p < 0.01$.

Abbreviations: FOS: fructo-oligosaccharides.

SUMMARY OF ENERGY PRODUCTION OF NONDIGESTIBLE SUGAR SUBSTITUTES

Figure 2 summarizes the fact that nondigestible sugar substitutes are metabolized through the fermentation by intestinal bacteria. Digestible carbohydrates such as sucrose, maltose, and starch are hydrolyzed to monosaccharides such as glucose and fructose by intestinal digestive enzymes, absorbed from the small intestine, and then metabolized in the body. In contrast, orally ingested nondigestible sugar substitutes escape digestion and absorption in the small intestine and reach the large intestine, where they are completely fermented by intestinal bacteria. Then, the short-chain fatty acids produced by the intestinal bacteria are absorbed from the lower intestine and further metabolized by the host to produce the energy.

Hydrogen is also produced from sugar substitutes in the fermentation by intestinal bacteria and excreted to the breath. In addition, the blood glucose level does not increase in the ingestion of nondi-

gestible sugar substitutes, because glucose is not produced in the fermentation. For example, when cellobiose, which is a nondigestible saccharide, was orally administered in healthy female subjects, breath hydrogen was clearly excreted, but blood glucose level did not increase. In contrast, absorbable glucose, which was orally administered, greatly increased blood glucose level, but it did not exhale breath hydrogen (unpublished data).

Figure 3 summarizes the metabolism of nondigestible sugar substitutes in the large intestine [7]. Sugar substitutes that are not digested in the small intestine reach the large intestine where they are completely fermented by intestinal bacteria. Short-chain fatty acids such as acetic acid, propionic acid and butyric acid, carbon dioxide, methane, and hydrogen are produced as end-products of the fermentation. A part of the sugar substitute is incorporated into the component of intestinal bacteria and then metabolized.

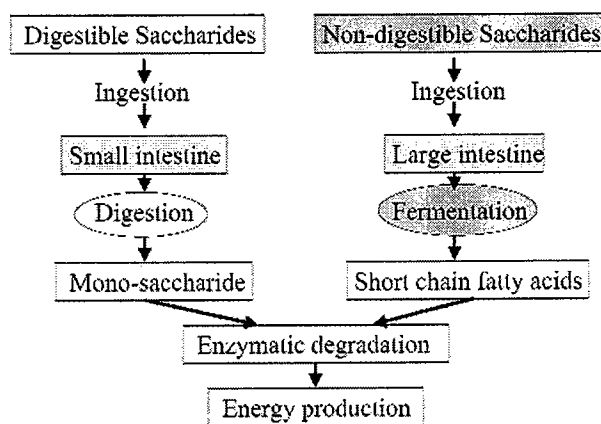


Fig. 2 Pathway of energy production from nondigestible sugar substitutes.

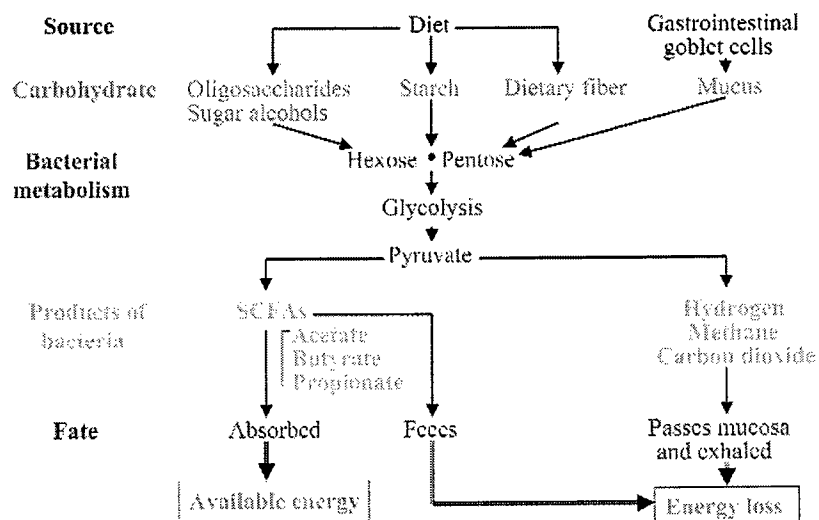


Fig. 3 Carbohydrate metabolism in the large intestine.

Short-chain fatty acids produced are readily absorbed from the lower intestine and further metabolized to carbon dioxide to provide energy for the host. Carbon dioxide, hydrogen, and methane are not further metabolized and excreted to breath, flatus, and feces.

Only short-chain fatty acids can contribute to energy production.

ESTIMATION OF AVAILABLE ENERGY OF NONDIGESTIBLE SUGAR SUBSTITUTES

As mentioned above, the available energy from nondigestible sugar substitutes cannot be estimated by currently used methods for common foods. Therefore, I would like to introduce method (1), which evaluates the available energy of nondigestible and/or nonabsorbable sugar substitutes according to several fermentation equations proposed previously [8–11].

When the combustion energy of each short-chain fatty acid is taken into consideration in the calculation of these equations in Table 3, the total energy of short-chain fatty acids produced by intestinal bacteria can be calculated. The total energy obtained from 4 fermentation equations was between 2.51 and 2.86 kcal/g, and the variation was very small, in spite of the fermentation equations being very different. The average value was 2.71 kcal/g [1,12]. The result also indicates that the potential energy decreased from 4 to 2.71 kcal/g, if the orally ingested saccharide is completely fermented by intestinal bacteria.

On the other hand, when ^{14}C -non-digestible sugar substitutes were orally administered to human subjects, about 15 % of the total radioactivity was excreted into the feces [13,14]. Therefore, the metabolizable energy was calculated as 2.3 kcal/g from 2.71 times 0.85. Also, the results obtained from animal experiments using the diet, in which the digestible saccharide was replaced by nondigestible saccharide, demonstrate that the metabolizable energy is approximately 2 to 2.3 kcal/g [15–17].

I would like to propose that the available energy of nondigestible sugar substitutes, which escape digestion and absorption in the small intestine and are completely fermented by intestinal bacteria in the gastrointestinal tract, is 2 kcal/g as energy coefficient. This value is approximately 50 % of the value of sucrose. I think that this value, 2 kcal/g, is practical and sufficient for nutrition education. This value has been used already to evaluate the energy of processed foods in the Nutrition Improvement ACT in Japan [18].

Table 4 is a summary of energy coefficients of sugar substitutes, which are listed in the Nutrition Improvement ACT in Japan. Available energy of erythritol is 0 kcal/g, because more than 90 % of orally ingested erythritol is readily absorbed from the small intestine and excreted into the urine without any degradation. Erythritol, which is not absorbed from the small intestine, is fermented by intestinal bacteria. Xylitol and sorbitol are partially absorbed from the small intestine and metabolized in the body. Thus, the available energy is 3 kcal/g.

Table 3 Proposed equations for colonic fermentation of carbohydrates and energy estimation.

I	$58 \text{ C}_6\text{H}_{12}\text{O}_6 \rightarrow 62 \text{ Acet} + 22 \text{ Prop} + 16 \text{ But}$ $+ 60.5 \text{ CO}_2 + 33.5 \text{ CH}_4 + 27 \text{ H}_2\text{O}$	2.78 kcal/g	[8]
II	$34.5 \text{ C}_6\text{H}_{12}\text{O}_6 \rightarrow 48 \text{ Acet} + 11 \text{ Prop} + 5 \text{ But}$ $+ 34.25 \text{ CO}_2 + 23.75 \text{ CH}_4 + 10.5 \text{ H}_2\text{O}$	2.70 kcal/g	[9]
III	$58 \text{ C}_6\text{H}_{12}\text{O}_6 + 36 \text{ H}_2\text{O} \rightarrow 60 \text{ Acet} + 24 \text{ Prop} + 16 \text{ But}$ $+ 92 \text{ CO}_2 + 256 [\text{H}]$	2.86 kcal/g	[11]
IV	$37.73 \text{ C}_6\text{H}_{12}\text{O}_6 \rightarrow 34.5 \text{ Acet} + 9.7 \text{ Prop} + 8.6 \text{ But}$ $+ 38.2 \text{ CO}_2 + 18.8 \text{ CH}_4 + 6.13 \text{ C}_6\text{H}_{10}\text{O}_3$	2.51 kcal/g	[10]

Table 4 Available energy of saccharides.

Available energy	Saccharides
0 (≤ 0.4)	Erythritol ^a
1 (0.5–1.4)	Polydextrose
2 (1.5–2.4)	Sorbose, mannitol ^a Galactopyranosyl(β_{1-3})glucopyranose, galactopyranosyl(β_{1-6})glucopyranose, xylobiose, gentiobiose, lactulose, isomaltitol ^a , palatinol ^a , maltitol ^a , lactitol ^a galactosyl-sucrose, 4'galactosyl-lactose, 6'galactosyl-lactose, xylotriase, kestose, gentiotriose, raffinose, maltotriitol ^a , stachyose, nystose, gentiotetraose, fructofranosylnystose α -cyclodextrin, β -cyclodextrin, maltosyl β -cyclodextrin
3 (2.5–3.4)	Sorbitol ^a , xylitol ^a Theande-oligosaccharide, palatinose-oligosaccharide, soybean-oligosaccharide ^b
4 (≥ 3.5)	Glucose, fructose, galactose, sucrose, maltose, lactose, trehalose, trehalulose, isomaltose, palatinose, isomaltotriose, panose, maltotriose, glucosyl-sucrose, maltosyl-sucrose, maltotetraose

^aSugar alcohols; ^braffinose and stachyose 30 %, sucrose 50 %, others 20 %.

MAXIMUM PERMISSIBLE DOSE OF SUGAR SUBSTITUTES

A sufficiently high ingestion of nondigestible sugar substitutes regularly causes overt diarrhea in human and animals. This diarrhea is due to osmogenic retention of fluid in both the small and large intestines. However, the diarrhea disappears in rats within a few days, because intestinal bacteria, which readily utilize these saccharides, increases during repeated ingestion and quickly decomposes them.

Tolerance of the ingestion of these sugar substitutes, expressed as the relation between dose levels and symptoms, shows considerable individual variation. In order to estimate the transitory laxative threshold of test substances, the minimal amount of ingestion of the test substance that caused diarrhea was calculated for the individual subject. These values were used to calculate the cumulative incidence of diarrhea. Figure 4 shows the relationship between several dose levels of trehalose or lactulose and diarrhea incidence in all subjects [19]. The correlation between trehalose intake and diarrhea incidence was expressed in an equation ($y = 79 \times -51$) as shown in Fig. 4. The point at which this straight line

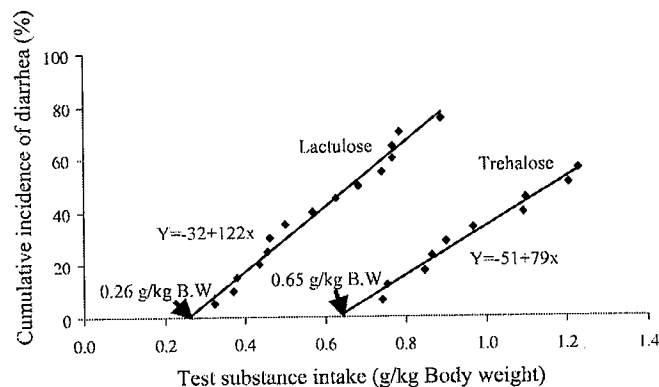


Fig. 4 Correlation between the ingestion of trehalose or lactulose and diarrhea incidence in healthy subjects. The minimal amount (g/kg body weight) of test substance that caused diarrhea was calculated for each individual subject; then the cumulative frequency of diarrhea was calculated in order from the smaller value. From the correlation equation between test substance intake and diarrhea incidence, the maximal noneffective dosage for diarrhea was estimated.

crosses the x-axis, namely the x coordinate of 0 % of diarrhea incidence, indicates the transitory laxative threshold. From this equation, the maximum permissible dose level of trehalose was estimated as 0.65 g/kg body weight, and that of lactulose was 0.26 g/kg body weight.

Table 5 summarizes the maximum permissible dose at which transitory diarrhea is not caused by the ingestion of nondigestible sugar substitutes for Japanese adults [1,2]. The maximum permissible dose of trehalose is greater than that of lactulose, because trehalose is partially hydrolyzed by small intestinal enzymes, while lactulose is not hydrolyzed. The acceptable value of sugar substitutes, which are not hydrolyzed by digestive enzymes, is approximately 0.3 g/kg body weight in our experiments using healthy human subjects. That is, the permissible dose level of the person with 50 kg of body weight is calculated as 15 g per ingestion. This means that nothing causes diarrhea until 15 g ingestion of nondigestible sugar substitutes.

The value in Table 5 is the summary of the maximum permissible dose level per kg body weight in single ingestion. The value changes depending on digestibility and absorbability of sugar substitutes. Also, it is varied by some factors such as the separate ingestion, twice or more times in a day, property of test substance, and the acclimation to test substance after repeated ingestion. For example, the maximum permissible dose level increased to about 1.5 times, after one container of chocolate containing lactitol in a day was repeatedly ingested by health female subjects for 10 days (unpublished data).

A sufficiently high ingestion of nondigestible sugar substitutes regularly causes overt diarrhea due to osmogenic retention of fluid. Therefore, it is essential to estimate the maximum permissible dose level of nondigestible sugar substitutes used in processed foods.

Table 5 Maximum permissible dose of sugar substitutes not causing transitory diarrhea.

Sugar substitutes	Maximum permissible dose (g/kg body wt)	
	Male	Female
Erythritol	0.66	0.80
Xylitol	—	0.7
Sorbitol	0.17	0.24
	0.15 ^a	0.3 ^a
Maltitol	—	0.30
	0.3 ^a	0.3 ^a
Lactitol	—	0.37
Palatinit	0.3 ^d	—
Trehalose	—	0.65
Cellobiose	—	0.36
Lactulose	—	0.32
Galactosyl-sucrose	0.6 ^b	0.6 ^b
	—	0.8
4'Galacto-oligosaccharide	0.28 ^c	0.14 ^c
6'Galacto-oligosaccharide	0.3 ^e	0.3 ^e
Xylo-oligosaccharide	0.12 ^f	—
Fructo-oligosaccharides	—	0.34
	0.3 ^e	0.4 ^c
Isomalto-oligosaccharides	>1.5 ^c	—
Soybean-oligosaccharides	0.64 ^c	0.96 ^c

^aKoizumi et al.; ^bMikuni et al.; ^cHata et al.; ^dMitsui Sugar Co.; ^eYakult Co., Ltd.;

^fSuntory Co., Ltd.

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